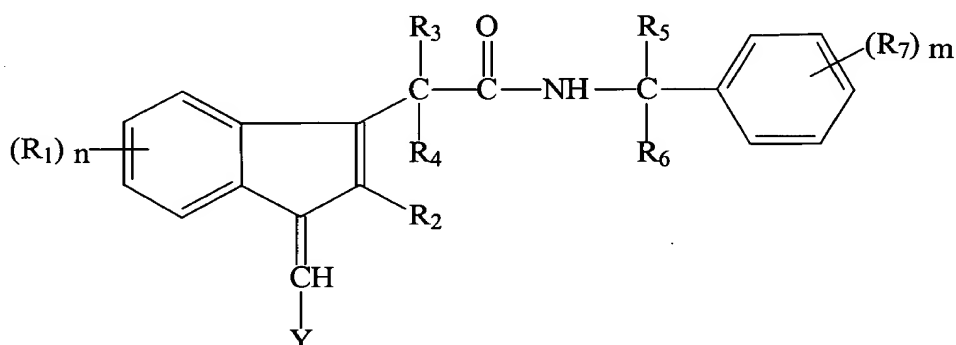


WE CLAIM:

1. A method of treating scleroderma in a mammal with that disease comprising administering to the mammal a physiologically effective amount of an inhibitor of PDE2 wherein said inhibitor does not substantially inhibit COX I or COX II.
2. The method of claim 1 wherein mammal is also administered an inhibitor of PDE5.
3. The method of claim 2 wherein said inhibitor of PDE2 and PDE5 comprise the same compound.
4. The method of claim 1 wherein said inhibitor is administered without an NSAID.
5. The method of claim 1 wherein said inhibitor has an  $IC_{50}$  for PDE2 of no more than about 25  $\mu$ M. and has an  $IC_{50}$  for each of the COX enzymes greater than about 40  $\mu$ M.
6. A method of treating scleroderma in a mammal comprising administering to the mammal a compound of the formula:



wherein  $R_1$  is independently selected in each instance from the group consisting of hydrogen, halogen, lower alkyl, loweralkoxy, amino, loweralkylamino, di-loweralkylamino, loweralkylmercapto, loweralkyl sulfonyl, cyano, carboxamide, carboxylic acid, mercapto, sulfonic acid, xanthate and hydroxy;

$R_2$  is selected from the group consisting of hydrogen and lower alkyl;

$R_3$  is selected from the group consisting of hydrogen, halogen, amino, hydroxy, lower alkyl amino, and di-loweralkylamino;

$R_4$  is hydrogen, or  $R_3$  and  $R_4$  together are oxygen;

TOP SECRET - CONFIDENTIAL

TOP SECRET - CONFIDENTIAL

TOP SECRET - CONFIDENTIAL

TOP SECRET - CONFIDENTIAL

TOP SECRET - CONFIDENTIAL

TOP SECRET - CONFIDENTIAL

TOP SECRET - CONFIDENTIAL

TOP SECRET - CONFIDENTIAL

TOP SECRET - CONFIDENTIAL

TOP SECRET - CONFIDENTIAL

TOP SECRET - CONFIDENTIAL

TOP SECRET - CONFIDENTIAL

TOP SECRET - CONFIDENTIAL

15. The method of claim 13 wherein  $R_3$  is selected from the group consisting of hydrogen, hydroxy and lower alkylamino.
16. The method of claim 6 wherein  $R_5$  and  $R_6$  are independently selected from the group consisting of hydrogen, hydroxy-substituted lower alkyl, amino lower alkyl, lower alkylamino-lower alkyl, lower alkyl amino di-lower alkyl,  $-\text{CO}_2\text{H}$ ,  $-\text{C}(\text{O})\text{NH}_2$ .
17. The method of claim 15 wherein  $R_5$  and  $R_6$  are independently selected from the group consisting of hydrogen, hydroxy-substituted lower alkyl, amino lower alkyl, lower alkylamino-lower alkyl, lower alkyl amino di-lower alkyl,  $-\text{CO}_2\text{H}$ ,  $-\text{C}(\text{O})\text{NH}_2$ .
18. The method of claim 6 wherein  $R_5$  and  $R_6$  are independently selected from the group consisting of hydrogen, hydroxy-substituted lower alkyl, lower alkyl amino di-lower alkyl,  $-\text{CO}_2\text{H}$ ,  $-\text{C}(\text{O})\text{NH}_2$ .
19. The method of claim 17 wherein  $R_5$  and  $R_6$  are independently selected from the group consisting of hydrogen, hydroxy-substituted lower alkyl, lower alkyl amino di-lower alkyl,  $-\text{CO}_2\text{H}$ ,  $-\text{C}(\text{O})\text{NH}_2$ .
20. The method of claim 6 wherein  $R_7$  is independently selected in each instance from the group consisting of hydrogen, lower alkoxy, hydroxy, amino, lower alkyl amino, di-lower alkyl amino, halogen,  $-\text{CO}_2\text{H}$ ,  $-\text{SO}_3\text{H}$ ,  $-\text{SO}_2\text{NH}_2$ , amino lower alkyl, and  $-\text{SO}_2(\text{lower alkyl})$ .
21. The method of claim 19 wherein  $R_7$  is independently selected in each instance from the group consisting of hydrogen, lower alkoxy, hydroxy, amino, lower alkyl amino, di-lower alkyl amino, halogen,  $-\text{CO}_2\text{H}$ ,  $-\text{SO}_3\text{H}$ ,  $-\text{SO}_2\text{NH}_2$ , amino lower alkyl, and  $-\text{SO}_2(\text{lower alkyl})$ .
22. The method of claim 6 wherein  $R_7$  is independently selected in each instance from the group consisting of hydrogen, lower alkoxy, hydroxy, amino, halogen,  $-\text{CO}_2\text{H}$ ,  $-\text{SO}_3\text{H}$ ,  $-\text{SO}_2\text{NH}_2$ , amino lower alkyl, and  $-\text{SO}_2(\text{lower alkyl})$ .
23. The method of claim 18 wherein  $R_7$  is independently selected in each instance from the group consisting of hydrogen, lower alkoxy, hydroxy, amino, halogen,  $-\text{CO}_2\text{H}$ ,  $-\text{SO}_3\text{H}$ ,  $-\text{SO}_2\text{NH}_2$ , amino lower alkyl, and  $-\text{SO}_2(\text{lower alkyl})$ .
24. The method of claim 22 wherein at least one of the  $R_7$  substituents is ortho- or para-located.
25. The method of claim 23 wherein at least one of the  $R_7$  substituents is ortho- or para-located.

26. The method of claim 24 wherein at least one of the R<sub>7</sub> substituents is ortho-located.

27. The method of claim 25 wherein at least one of the R<sub>7</sub> substituents is ortho-located.

28. The method of claim 6 wherein Y is selected from the group consisting of quinolinyl, isoquinolinyl, pyridinyl, pyrimidinyl and pyrazinyl or said substituted variants thereof.

29. The method of claim 6 wherein said compound comprises (Z)-5-fluoro-2-methyl-(4-pyridylidene)-3-(N-benzyl)indenylacetamide hydrochloride.

30. The method of claim 6 wherein said compound comprises (Z)-5-fluoro-2-methyl-(4-pyridylidene)-3-(N-benzyl)-indenylacetamide p-methylbenzenesulfonate.

31. A method of inhibiting activated macrophages in a mammal with scleroderma comprising chronically administering to the mammal a physiologically effective amount of an inhibitor of PDE2.

32. The method of claim 31 wherein mammal is also administered an inhibitor of PDE5.

33. The method of claim 32 wherein said inhibitor of PDE2 and PDE5 comprise the same compound.

34. The method of claim 31 wherein said inhibitor does not substantially inhibit COX I or COX II.

35. The method of claim 33 wherein said inhibitor does not substantially inhibit COX I or COX II.

36. The method of claim 31 wherein the mammal is a companion pet.

37. The method of claim 36 wherein the mammal is human.

38. A method of treating scleroderma in a mammal with that disease comprising inhibiting PDE2 in the diseased tissue without substantially inhibiting COX I or COX II.

39. A method of treating scleroderma in a mammal with that disease comprising inhibiting PDE2 in the diseased tissue.

40. A method of inhibiting activated macrophages in a mammal with scleroderma comprising chronically administering to the mammal a physiologically

effective amount of an ~~inhibitor~~ of PDE2 having a PDE2 IC<sub>50</sub> no more than about 25  $\mu$ M and having a COX IC<sub>50</sub> greater than about 40  $\mu$ M.

09938160-082301